**exon 6** in 73 FCHL family members demonstrated the presence of a single nucleotide polymorphism with two alleles, coding for methionine (196M) and arginine (196R). Complete **linkage disequilibrium** between CA267, CA271 and CA273 and this polymorphism was detected. In 85 hyperlipidemic FCHL subjects, an association was demonstrated between soluble **TNFRSF1B** plasma concentrations and the CA271-196M haplotype. In conclusion, **TNFRSF1B** was found to be associated with susceptibility to FCHL. Our data suggest that an as yet unknown disease-associated mutation, linked to alleles 196M and CA271, plays a role in the pathophysiology of FCHL.

=> d hist

(FILE 'HOME' ENTERED AT 15:37:32 ON 24 OCT 2003)

FILE 'MEDLINE, BIOSIS, CAPLUS' ENTERED AT 15:37:43 ON 24 OCT 2003

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L1          887 S TNFBR OR TNFR80 OR TNFRSF1B OR CD1206 OR TNFR2
L2          791 S TNFR2
L3           58 S L1 AND CHRON?
L4          151 S L1 AND (POLYMORPH? OR SNP?)
L5            2 S L4 AND L3
L6            2 DUP REM L5 (0 DUPLICATES REMOVED)
L7           38 S L1 AND EXON (1A) 6
L8           18 DUP REM L7 (20 DUPLICATES REMOVED)
L9            4 S L8 AND LINKAGE(1A) DISEQUIL?
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d ibib ab 1-4

L9 ANSWER 1 OF 4 MEDLINE on STN
ACCESSION NUMBER: 2002459335 MEDLINE
DOCUMENT NUMBER: 22206407 PubMed ID: 12217957
TITLE: **Linkage disequilibrium** between polymorphisms in the human **TNFRSF1B** gene and their association with bone mass in perimenopausal women.
AUTHOR: Albagha Omar M E; Tasker Paul N; McGuigan Fiona E A; Reid David M; Ralston Stuart H
CORPORATE SOURCE: Department of Medicine and Therapeutics, University of Aberdeen, Foresterhill, Aberdeen, UK.
SOURCE: HUMAN MOLECULAR GENETICS, (2002 Sep 15) 11 (19) 2289-95. Journal code: 9208958. ISSN: 0964-6906.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20020910
Last Updated on STN: 20030416
Entered Medline: 20030414

AB Osteoporosis is a multifactorial disease with a strong genetic component characterized by reduced bone density and increased fracture risk. A candidate locus for regulation of hip bone mineral density (BMD) has been identified on chromosome 1p36 by linkage analysis. One of the positional and functional candidate genes located within this region is the tumour necrosis factor receptor superfamily member 1B (**TNFRSF1B**). In order to investigate whether allelic variation in **TNFRSF1B** contributes to regulation of bone mass, we studied several polymorphisms of this gene in a population based cohort study of 1240 perimenopausal women from the UK. We studied a T676G change in **exon 6** (196: Met-Arg) and three SNPs (G593A, T598G, and T620C) in the 3'UTR of the gene. The 3'UTR SNPs were in strong **linkage disequilibrium** (LD) with each other (P<0.00001), and the **exon 6** SNP was in LD with G593A and T598G (P<0.00001). We found no association between T676G alleles and BMD at the spine or hip. However, haplotype analysis showed that subjects homozygous for the A593-T598-C620 haplotype (n=85) had femoral neck BMD values 5.7% lower than those who did not carry the haplotype (n=1155; P<0.00008) and this remained significant after correcting for confounding factors and multiple testing (P<0.0009). Regression analysis showed that the ATC haplotype accounted for 1.2% of the population variance in hip BMD and was the second strongest predictor after body weight. In summary, our work supports the view that allelic variation in the 3'UTR of **TNFRSF1B** gene contributes to the genetic regulation of bone mass, with effects that are specific for femoral neck BMD.

L9 ANSWER 2 OF 4 MEDLINE on STN
ACCESSION NUMBER: 2002451488 MEDLINE
DOCUMENT NUMBER: 22196962 PubMed ID: 12209506
TITLE: Association between tumor necrosis factor receptor II and familial, but not sporadic, rheumatoid arthritis: evidence for genetic heterogeneity.
COMMENT: Comment in: Arthritis Rheum. 2003 Jan;48(1):273-4
AUTHOR: Dieude Philippe; Petit Elisabeth; Cailleau-Moindrault Severine; Osorio Jose; Pierlot Celine; Martinez Maria; Faure Sabine; Alibert Olivier; Lasbleiz Sandra; De Toma Claudia; Bardin Thomas; Prum Bernard; Cornelis Francois
CORPORATE SOURCE: GenHotel, Evry-Genopole, France. (European Consortium on Rheumatoid Arthritis Families). dieude@polyarthrite.net
SOURCE: ARTHRITIS AND RHEUMATISM, (2002 Aug) 46 (8) 2039-44. Journal code: 0370605. ISSN: 0004-3591.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020906
Last Updated on STN: 20030225
Entered Medline: 20020919

AB OBJECTIVE: Tumor necrosis factor alpha (TNFalpha) binds the receptors TNFRI and TNFRII. Results of genome scans have suggested that **TNFR2** is a candidate rheumatoid arthritis (RA) locus. A case-control study in a UK Caucasian population has shown an association between a **TNFR2** genotype (196R/R in **exon 6**) and familial, but not sporadic, RA. The present study was undertaken to test this association in the French Caucasian population. METHODS: To test for an association in sporadic RA, 100 families were genotyped for the 196M/R polymorphism and analyzed using the transmission disequilibrium test and haplotype relative risk. To test for an association in familial RA, RA index cases from 100 affected sibpair (ASP) families were genotyped for 196M/R. Linkage analysis was performed with 3 **TNFR2** microsatellite markers. RESULTS: The **TNFR2** 196R/R genotype was not associated with sporadic RA (odds ratio [OR] 0.59, P = 0.72), but was associated with familial RA (OR 4.0, P = 0.026). The association was most marked in the context of **TNFR2** "twin-like" RA sibs (affected sibs sharing both **TNFR2** haplotypes) (OR 9.2, P = 0.0017). Linkage analysis results were consistent with the association; most of the **TNFR2** linkage evidence was found in the subgroup of families with 196R/R ASP index cases. CONCLUSION: This study is the first to replicate evidence of the involvement of **TNFR2** in RA genetic heterogeneity. Our data refine the initial hypothesis, to suggest that a **TNFR2** recessive factor, in **linkage disequilibrium** with the 196R allele, plays a major role in a subset of families with multiple cases of RA.

L9 ANSWER 3 OF 4 MEDLINE on STN
ACCESSION NUMBER: 2002407046 MEDLINE
DOCUMENT NUMBER: 22151311 PubMed ID: 12161545
TITLE: Comment: the methionine 196 arginine polymorphism in **exon 6** of the TNF receptor 2 gene ( **TNFRSF1B**) is associated with the polycystic ovary syndrome and hyperandrogenism.
AUTHOR: Peral Belen; San Millan Jose L; Castello Roberto; Moghetti Paolo; Escobar-Morreale Hector F
CORPORATE SOURCE: Instituto de Investigaciones Biomedicas, Consejo Superior de Investigaciones Cientificas, 28029 Madrid, Spain.
SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, (2002 Aug) 87 (8) 3977-83.
Journal code: 0375362. ISSN: 0021-972X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020806
Last Updated on STN: 20020831
Entered Medline: 20020830

AB Inflammatory cytokines such as TNF alpha may play a role in the pathogenesis of common metabolic disorders, including hyperandrogenism and the polycystic ovary syndrome (PCOS). The TNF receptor 2 mediates most of the metabolic effects of TNF alpha. In the present study, we have evaluated serum soluble TNF receptor 2 levels, and several common polymorphisms in the TNF receptor 2 gene (**TNFRSF1B**), in women presenting with PCOS or hyperandrogenic disorders. Initial studies included 103 hyperandrogenic patients (42 presenting with PCOS) and 36 controls from Spain. The 196R alleles of the M196R (676 T-->G) variant in

**exon 6** of **TNFRSF1B**, which is in **linkage disequilibrium** with a CA-repeat microsatellite polymorphism in intron 4 of **TNFRSF1B**, tended to be more frequent in hyperandrogenic patients than in controls (P = 0.056), reaching statistical significance when the analysis was restricted to include only PCOS patients (P < 0.03). Extended analysis including another 11 hyperandrogenic patients from Spain and 64 patients and 29 controls from Italy confirmed the association between 196R alleles of the M196R variant and hyperandrogenic disorders (P < 0.05), which was maintained when restricting the analysis to PCOS patients (P < 0.02). On the contrary, the 3'-untranslated region (exon 10) variants 1663 G-->A, 1668 T-->G, and 1690 T-->C were not associated with hyperandrogenism. The soluble TNF receptor 2 levels were not different between patients and controls but were increased in obese subjects, compared with lean individuals, and were affected by the interaction between the 1663 G-->A and 1668 T-->G variants in the 3'-untranslated region of **TNFRSF1B**. The **TNFRSF1B** genotype did not influence any clinical or biochemical variable related to hyperandrogenism or insulin sensitivity and was not associated with obesity, both in hyperandrogenic patients and healthy controls considered separately. In conclusion, the M196R (676 T-->G) variant in **exon 6** of **TNFRSF1B** is associated with hyperandrogenism and PCOS, further suggesting a role for inflammatory cytokines in the pathogenesis of these disorders.

L9 ANSWER 4 OF 4 MEDLINE on STN
ACCESSION NUMBER: 2001028391 MEDLINE
DOCUMENT NUMBER: 20414628 PubMed ID: 10958645
TITLE: Identification of **TNFRSF1B** as a novel modifier gene in familial combined hyperlipidemia.
AUTHOR: Geurts J M; Janssen R G; van Greevenbroek M M; van der Kallen C J; Cantor R M; Bu X; Aouizerat B E; Allayee H; Rotter J I; de Bruin T W
CORPORATE SOURCE: Laboratory of Molecular Metabolism and Endocrinology, Department of Internal Medicine, Cardiovascular Research Institute Maastricht, Academic Hospital, Maastricht University, PO Box 616, 6200 MD, Maastricht, The Netherlands.. j.guerts@intmed.unimaas.nl
CONTRACT NUMBER: HL-28481 (NHLBI)
P41 RR03655 (NCRR)
SOURCE: HUMAN MOLECULAR GENETICS, (2000 Sep 1) 9 (14) 2067-74. Journal code: 9208958. ISSN: 0964-6906.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001121

AB Familial combined hyperlipidemia (FCHL) is the most commonly inherited hyperlipidemia in man, with a frequency of +/-1% in the general population and approximately 10% in myocardial infarction survivors. A genomic scan in 18 Dutch FCHL families resulted in the identification of several loci with evidence for linkage. One of these regions, 1p36.2, contains **TNFRSF1B** which encodes one of the tumor necrosis factor receptors. An intron 4 polymorphic CA-repeat was used to confirm linkage to FCHL. Linear regression analysis using 79 independent sib pairs showed linkage with a quantitative FCHL discriminant function (P = 0.032), and, borderline, with apolipoprotein B levels (P = 0.064). Furthermore, in a case-control study, association was demonstrated since the overall CA-repeat genotype distribution was significantly different among 40 unrelated FCHL patients and 48 unrelated healthy spouse controls (P = 0.029). This difference was due to a significant increase in allele CA271 homozygotes in the FCHL patients (P = 0.019). Mutation analysis of